The NIH Neuroscience Blueprint:
Building Collaboration and a Toolkit for the Future

Diseases of the nervous system pose a significant public health and economic challenge, affecting nearly one in three Americans at some point in life, with a cost exceeding $500 billion per year. The National Institutes of Health (NIH) Neuroscience Blueprint is a collaborative effort across 14 Institutes and Centers to accelerate the pace of discovery and understanding in neuroscience research. The Neuroscience Blueprint will build on current efforts at the NIH and, with input from the scientific community, address the need for new scientific resources and tools that would benefit all neuroscience research. More collaboration and better tools—these are the cornerstones of the NIH Neuroscience Blueprint and the keys to future breakthroughs that will prevent and reduce the burden of diseases of the nervous system.

PARTICIPANTS:

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Rationale

The human nervous system has more than a trillion cells, many of which have more than a thousand connections; it is remarkable in its complexity. The nervous system is responsible for diverse functions, from our behavior, perceptions, thoughts, and feelings, to regulating heart rate, muscle tone, and immune function. Understanding how the nervous system develops, works, and ages— in both health and disease —is the challenge facing neuroscientists. At least 1000 diseases affect the nervous system, leading to more hospitalizations than any other disease group and, according to the World Health Organization, accounting for six of the top ten sources of disability from all medical causes in the U.S. Approximately one in three Americans will be affected by a disease of the nervous system at some point in life. As the world's largest supporter of research on the nervous system, the NIH seeks to accelerate the pace of discovery in neuroscience to address this costly public health challenge.

Understanding the Nervous System and its Diseases

Fortunately, this is an auspicious time for biomedical and behavioral research on the nervous system. With advances in genomic mapping, increasingly sophisticated neuroimaging tools, and a wide range of model organisms, profound insights into the nervous system and how it works are possible. Responding to the public health need and the scientific potential of the moment, 14 NIH Institutes and Centers have joined to initiate the NIH Neuroscience Blueprint. The Blueprint will better coordinate existing efforts to spur discovery and create resources and a toolkit for all neuroscientists to use. Complementing the individual strategic plans of each participating Institute or Center, the Blueprint effort will selectively and collaboratively invest in additional research that benefits the entire neuroscience community, in turn yielding discoveries that benefit the public's health.

This objective will be achieved by focusing on tools and resources that will best advance research on three linked processes that underlie health and all disorders of the nervous system.

These processes are: (1) **development** through the lifespan—including factors that control cell specialization, signals that guide the formation of connections among nerve cells, and mechanisms by which genes and experience work to sculpt the nervous system and behavior; (2) **neurodegeneration** – loss of connections or cell death from disease and normal aging; and (3) **plasticity** - the ability to change and adapt in response to environmental cues, experience, injury, and disease. Research on these common processes should inform treatments for diverse disorders of the nervous system. For example, determining the mechanisms for normal development of the nervous system is crucial for efforts to regenerate or replace cells lost in Parkinson's disease, spinal cord injury, or age-related hearing loss. Studies on cell death will prove instructive for macular degeneration, Alzheimer's disease, and childhood-onset schizophrenia, and insights from one disease should inform our understanding of others. Neuroscience research tells us that the brain never stops changing. This capacity to adapt underlies memory and imagination. However, plasticity may become maladaptive in depression, dystonia, substance abuse, obesity, and chronic pain.

Understanding each of these processes requires a multi-level approach. In consultation with the research community, we have identified five strategic levels where the development, acceleration, and coordination of enabling resources will yield progress for our understanding of the development, degeneration, and plasticity of the nervous system:

- Molecular: Discovering the key molecules for nervous system function
- Cellular: Charting the life, death, and specialization of cells in the nervous system
- Systems: Identifying functional circuits for perception, cognition, emotion, and behavior, as well as those that regulate bodily functions
- Translational: Developing interventions for maintaining health and reducing the burden of disease; and
- Integrative: Sharing ideas and resources to promote discovery

Each of these levels will be discussed below, with areas of ongoing and potential collaboration among the Institutes and Centers.

The Neuroscience Blueprint: Building Collaboration and a Toolkit for the Future

The Blueprint emphasizes collective action as an integral part of how each participating Institute and Center pursues its mission. This means resource gaps and needed tools can be addressed to a far greater extent than would be possible by a single Institute, enriching the neuroscience community and changing the landscape of research. The NIH is uniquely positioned to lead this effort to spur the pace of discovery for the good of public health.

Molecular: Discovering the key molecules for nervous system function

Development, degeneration, and plasticity all rest on the timely, regional expression of specific genes and proteins. Increasingly, we realize that the difference between health and disease may reflect subtle changes that, under certain environmental conditions, lead to protein expression at the wrong time, in the wrong place, or in the wrong amount. Discovering the changes in genes and proteins associated with health and disease is already providing targets for new treatments, for biomarkers, and for diagnostic tests, and will ultimately provide measures of risk that can inform strategies for prevention of nervous system diseases. With the mapping of the human genome and its haplotypes, we have unprecedented traction for understanding how, where, and when genetic variation confers risk for disease or resilience. Yet, we still have not identified the neuroanatomical location, the developmental timing, or the cellular function of most of the genes and proteins expressed in the brain, what we call the "neurogenome" and "neuroproteome," respectively. As we look to the future, participating Institutes and Centers have identified several projects underway that can be expanded to accelerate discoveries about the neurogenome and neuroproteome.

Neuroscience Blueprint Collaborations

- Mapping the neurogenome: GENSAT, an initiative to create and analyze transgenic mice to map gene expression and activity to different cell types and regions of the mouse central nervous system, has catalogued in a public database 1,000 genes by in situ hybridization and 300 genes in BAC (bacterial artificial chromosomes) transgenic mice. The Blueprint will expand this kind of effort to include gene expression in the eye and ear, and accelerate it by increasing the number of genes.
- Function of the neurogenome: To identify the physiological and behavioral functions of each neural gene, a public repository of mutant mice should be developed, building on the current Mutant Mouse Research Resource Centers and the Neuromice Consortium. These mice can accelerate the research of physiologists and behavioral scientists who have been delayed by having to develop their own transgenic animals.
- Tools for manipulating the genome: While a number of tools have been developed for changing gene expression in mice and Drosophila (fruit flies), functional studies of the nervous system have traditionally focused on rats, monkeys, and humans. New tools, such as RNAi and cDNA libraries, should be developed for the latter.
- Informatics: Support for informatics and imaging tools, such as a digital atlas of the brain to display molecular findings, is necessary to better understand how genes and proteins function and ultimately affect behavior and health.

Future possibilities: A public bank of antibodies generated against nervous system proteins, tools for altering genes in specific neural circuits, and novel approaches for manipulating more than one gene at a time are all recommendations for future Blueprint activities.

<u>Cellular: Charting the life, death, and specialization of cells in the nervous system</u>

The nervous system comprises hundreds of different types of cells, which serve different functions in development, degeneration, and plasticity. Many of these cell populations are affected selectively by diseases. For instance, motor neurons die selectively in ALS (Lou Gehrig's disease), light-sensitive neurons in macular degeneration, hair cells in hearing loss, dopamine cells in Parkinson's disease and drug abuse, and acetylcholine cells in Alzheimer's disease. The advent of stem cell research offers the possibility of replacing cells lost in these diseases. To harness the potential of stem cells, neuroscientists need to know how mature neurons develop and function, what is necessary to properly integrate new cells into neural circuits, and what happens to these cells in disease states, in response to injury, and during aging.

Neuroscience Blueprint Collaborations

- Stem cells as research tools: Currently, we know how to differentiate human embryonic stem cell lines into only a limited number of mature cell types. A stem cell study group is presently characterizing existing lines. The Blueprint could expand this effort by defining the conditions required to produce specific neural fates from human stem cells. Mouse embryonic stem cell lines with mutations that cause nervous system disorders can be used to study the effects of disease-associated mutations and to dissect the molecular pathways that control normal cellular development and behavior. The Blueprint could create a repository of cell lines for use by neuroscience investigators.
- Informatics: Two Blueprint Institutes support a Microarray Consortium for profiling gene expression in cells of the nervous system. The Blueprint could make this resource available to all neuroscience investigators. By optimizing the profiling of genes in individual cells and cataloguing these findings for the hundreds of different cell types, we hope to have a better understanding of the degree of specialization within the nervous system and possibly reveal why specific cells are vulnerable to injury or disease.

Future possibilities: Increasingly, the search for new treatments uses cell-based assays in a high throughput format. While this approach has been developed in other areas of medicine, the use of large-scale cell-based assays either for characterizing mutations associated with human disease or for screening small molecules remains to be optimized for the nervous system.

<u>Systems: Identifying functional circuits for perception, cognition, emotion, and behavior, as well as circuits that regulate bodily functions</u>

Nerve cells are organized into intricate circuits, and these circuits, in turn, into higher level networks. This connectivity and organization allows us to see, hear, think, and feel, while simultaneously regulating the essential bodily functions that are often beneath our awareness—until something goes wrong. Understanding how, where, and when these circuits and networks form and transform throughout life is one of the most complex and compelling challenges in neuroscience. With new techniques in imaging and physiological recording, we can study activity within circuits with unprecedented precision. These tools need to be optimized for studies of development, degeneration, and plasticity and the findings synthesized to achieve a better understanding of brain function in health and disease.

Neuroscience Blueprint Collaborations

- Data integration: Current programs are integrating neuroimaging data related to development and degeneration, such as the Neuroimaging Informatics Technology Initiative (NIfTI), the Pediatric MRI Study of Normal Development, and the Alzheimer's Disease Neuroimaging Initiative. These efforts involve data collection across multiple labs, and can be expanded and accelerated to provide needed imaging datasets for the neuroscience community.
- Informatics: Advances in technology and methods make this a promising time to develop even more informatics capacity, new neuroimaging and visualization tools, and better ways to integrate behavioral, functional, anatomical, and molecular data.

Future possibilities: Better tools are needed for imaging neural genes and proteins *in vivo*, including in the human brain. New PET ligands, new MRI methodologies, optical imaging, and multi-modality techniques need to be optimized for use not only in research, but also as clinical tools. In addition, we lack tools for detecting and integrating multi-unit signals reflecting neural activity, particularly electrical activity, with high spatial and temporal resolution, as well as standardized behavioral challenges for eliciting brain activity. The development of such tools would allow the study of neural processing in complex circuits serving perception, cognition, emotion, and behavior. Monitoring neural activity with imaging over the lifespan, across behavioral states, in response to drugs, and in states of health and disease is already providing critical insights into functional brain circuits. Bridging imaging signals to neural activity will be an important next step for understanding neural circuits.

Translational: Developing interventions for maintaining health and reducing the burden of disease

Reducing the public health burden of nervous system diseases is the ultimate goal of the Blueprint. One of the great challenges in the coming decade will be the translation of discoveries from molecular, cellular, and systems neuroscience into diagnostic tests, biomarkers, and strategies for prevention and treatment of disorders of the nervous system.

Neuroscience Blueprint Collaborations

- Coordination: A number of illnesses that affect the nervous system occur together (e.g., depression and Parkinson's disease, hair cell loss and retinal degeneration in Usher's disease) and many are addressed by multiple Institutes and Centers (e.g., pain, autism, Alzheimer's disease, Parkinson's disease). For some of these, trans-Institute working groups or committees exist to coordinate research efforts among the relevant Institutes and Centers. The Blueprint will identify other instances where working groups might be of benefit. The Participating Blueprint Institutes and Centers will also develop strategies to coordinate multi-systems clinical trials, focusing on co-morbidities and the use of multiple outcome measures where appropriate to maximize what can be learned.
- Informatics: The Blueprint will work with the NIH Roadmap to develop integrated data management for clinical trials with particular attention to inclusion of data concerning outcomes from multiple systems.
- Education: The translation of basic science discoveries into clinical benefit would be significantly enhanced by informing bench scientists (PhDs) about the neurobiology of disease and engaging them in addressing these challenges. Although some courses already exist with this goal, only a fraction of graduate students and postdoctoral fellows participate in them. The Blueprint will support the development of additional courses and training opportunities, encouraging efforts that cut across diseases and traditional departments.

Future possibilities: The neuroscience community has indicated a need for tools for therapeutics development. These include better animal models, new strategies for crossing the blood-brain barrier, biomarkers that predict treatment response, and repositories of tissues from people with various nervous system diseases.

<u>Integrative: Sharing ideas and resources to promote discovery</u>

Addressing the fundamental challenges of neuroscience will not only require new paradigms for studying molecules, cells, circuits, and the whole organism, but also better ways to integrate across these levels of analysis. Integration is especially difficult because it will require a change in research culture. Scientists from different disciplines speak different technical languages and frequently work in different departments at academic institutions. The National Neuroscience Center on the NIH campus in Bethesda, Maryland represents a new paradigm for bringing together researchers and sharing resources across several Institutes. The first phase of this facility, opened in 2004, groups NIH intramural investigators by research theme, irrespective of their Institute affiliation. The Blueprint seeks to develop similar interdisciplinary neuroscience programs extramurally. There is also a divide between basic neuroscience research and clinical research; few young neuroscientists with the most rigorous basic scientific training pursue research questions in clinical neuroscience, and few clinicians conduct research in fundamental mechanisms of health and disease. Although the development of new technologies has led to a proliferation of valuable information about the nervous system, much of this information is not readily accessed by people outside a narrow specialty, creating a barrier to the conduct of interdisciplinary research. If we are to accelerate advances in neuroscience, we need to change this environment.

Neuroscience Blueprint Collaborations

- Training: Currently, ten of the participating Blueprint Institutes and Centers support a collaborative training program for pre-doctoral fellows in neuroscience. Through this program, comprehensive training grants support broad, multidisciplinary training via basic neuroscience courses, laboratory rotations, and multidisciplinary classes. Identifying the best practices from existing programs and sharing this information will enable participating Institutes and Centers to build even stronger training programs.
- Educating the general public: For NIH-supported discoveries to reach their full potential, the public must be informed about them and educated about their significance. Each participating Institute and Center conducts public outreach and education campaigns for the disorders that fall within its mission. The Blueprint could increase coordination of these activities and the sharing of best practices to maximize the effectiveness of efforts to educate and build awareness.

Future possibilities: Progress in neuroscience could be enhanced by creating a program of research cores that would span traditional departments and the missions of multiple Institutes and Centers. A core grant may bring scientists together, for example, by focusing on one of the Neuroscience Blueprint themes--development, degeneration, or plasticity--and including both basic and clinical science relevant to these areas.

<u>Implementing the NIH Neuroscience Blueprint</u>

The Neuroscience Blueprint is ambitious in scope, spanning 14 Institutes and Centers, more than half of all the Institutes and Centers that make up the National Institutes of Health. Calling for an investment of $100 million over the next five years, the Blueprint is a collaborative process among Institutes and Centers and the research community. As the NIH looks to the future, the research community will help to identify resources and tools for future investment. Blueprint workgroups, with representatives from each Institute and Center, will continually assess progress and adapt the Blueprint to new discoveries and opportunities. Ultimately, success will be measured not by publications or patents, but by the impact on public health.

Conclusion

At certain critical points in the evolution of any discipline, it is helpful to ask: What are the roadblocks to progress? How can we accelerate discoveries? What are the most important priorities for our field? Neuroscience is at such a critical point. We now have the opportunity to map gene function and activity, to generate mature neurons from stem cells, and to explore complex information processing in the brain. Each of these advances will have profound public health significance, changing the way we prevent, diagnose, and treat diseases of the nervous system. In this document, we provide some of the plans under consideration for accelerating fundamental advances and for translating them to clinical practice. In these times of budgetary restraints, we can leverage existing efforts through relatively small contributions from each participating Neuroscience Blueprint Institute and Center and have a major impact. As noted at the outset, diseases of the nervous system present an enormous public health burden. This Blueprint represents the NIH commitment to reduce this burden by engaging the efforts of a talented and dedicated neuroscience research community.